

REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 1 and 3-5 are amended herein, to correct issues of grammar and to place the claims in proper U.S. format. Thus, no prohibited new matter is introduced by way of this Amendment.

Objections to the Specification and Claims

The title of the application is purportedly non descriptive. Thus, the title has been amended herein to further describe the invention. Applicants respectfully submit that the objection to the title has been obviated.

The claims are purportedly generally narrative and indefinite, failing to conform with current U.S. practice. However, the Office Action does not provide any specific explanation or examples as to how the present claims purportedly fail to conform to U.S. practice. Applicants have amended the claims herein, in the interest of expediting prosecution, to better conform with U.S. practice.

Claim Rejections 35 U.S.C. § 112, Second Paragraph

Claims 1, 3, 4 and 5 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 4 and 5 stand rejected for the recitation of "a carrier", as it is purportedly unclear as to whether the carrier is a buffer or a liposome. Applicants respectfully submit that the meaning of the term "carrier" is defined in the specification. Specifically, the specification, (*see* page 5, line 1) discloses that a carrier is a modified HPV-L1 protein devoid of type specific epitopes causing production of neutralizing antibodies. Thus, this rejection is obviated.

Claim 1 is further rejected for the recitation of "intentionally modified", as this term is purportedly indefinite. Applicants submit that this term is defined and discussed in the present specification as-filed. Specifically, "intentionally modified" is directed towards modification by substitution, but not deletion, of specific amino acids which are important for recognition of the polypeptide by antibodies. Applicants refer to the specification (page 6, line 5), which recites "modified to remove type-specific epitope(s) causing production of neutralizing antibodies." Applicants further note that as complete deletion of epitope sequences would change the conformation of the protein, it would be clearly necessary to remove the sequences by changing them, not deleting them. Thus, this rejection is obviated.

Claim 1 stands rejected for the recitation of the term "substance". Applicants submit that the skilled artisan would understand what is meant by "substance". Specifically, "substance" should be understood by the skilled artisan to refer to an amino acid sequence comprising of one or more T-cell epitopes, which are derived from any protein belonging to a group of proteins comprising tumor antigens, bacterial antigens, parasite antigens, viral antigens, or auto-antigens. As indicated throughout the specification (*see* especially page 5) the carrier protein is intended to carry peptides into a cell which illicit an immune response, and one skilled in the art would therefore understand the term "substance" to denote such a peptide. Thus, this rejection is obviated.

Claim 3 stands rejected for the recitation of "peptide", as it is purportedly unclear as to whether this term refers to a peptide HPV-L1 protein. Applicants note that "peptide" is defined throughout the specification and specifically on page 5, line 19. This term refers to amino acid sequences comprising one or more T-cell epitopes, which are derived from any protein(s) belonging to a group of proteins comprising tumor antigens, bacterial antigens, parasite antigens, viral antigens, or auto-antigens. The peptide is not an HPV-L1 protein, but may be an HPV protein, as indicated on page 5, line 19. Thus, this rejection is obviated.

Claim 4 stands rejected, as the intended T cell epitope is purportedly not defined. To this end, Applicants note that the intended T-cell epitopes may be derived from any proteins belonging to a group of proteins comprising tumor antigens, bacterial antigens, parasite antigens, viral antigens or auto-antigens, as disclosed on p. 6, line 11 of the

current specification. The T-cell epitope is not, however, from HPV-L1. This would be known to one skilled in the art given that the current claims are all directed to proteins attached to HPV-L1 peptides in which T-cell epitopes have been removed. The skilled artisan would not seek to reintroduce T-cell epitopes which had already been replaced.

Claim 5 stands rejected for the recitation of "derived" and "antigen comprising tumor". Applicants submit that "derived", as used in claim 5, is understood in the art. In support, Applicants submit the definition of "derivative" from *Stedman's Medical Dictionary*, 26th Ed., (1995) Williams and Wilkins: Baltimore, 461-462.

Regarding, "antigen comprising tumor", Applicants note that the claim is directed towards T-cell epitopes which derived from tumor, bacterial, parasitic, viral, or auto-antigens, *i.e.* the carrier may comprise a T-cell epitope sequence originating in any number of protein antigens. "A carrier according to claim 4, wherein said one or more T-cell epitopes are derived from a group of antigens comprising tumor, bacterial, parasite, viral or auto-antigens" can be reformulated as "a carrier according to claim 4, wherein said one or more T-cell epitopes comprise peptides derived from any protein(s) belonging to a group of proteins which comprises tumor antigens, bacterial antigens, parasite antigens, viral antigens or auto-antigens". Thus, this rejection is obviated.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1, 3, 4 and 5 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action states that there is no teaching in the specification about which "epitopes" or regions are removed, either "intentionally" or otherwise, to modify the L1 so it won't induce antibodies, or as to what peptides or epitopes or T-cell epitopes of tumor antigen is being fused to the so called modified L1 protein. Applicants respectfully traverse.

Applicants submit that the skilled artisan would be able to make and use the claimed invention based on what is disclosed in the specification as well as what is known in the art. To this end, Applicants direct the examiner to Christenson *et al.* (1994), submitted herewith, which discusses the known neutralizing epitopes present in HPV-L1. Christenson *et al.* discuss the highly conformational nature of the most neutralizing epitopes, thus the epitopes to be removed were clear to those knowledgeable in the art at the time of this invention. The epitopes to be fused to the protein are, as stated in the specification, any neutralizing antibody-inducing peptide sequences from the group comprising: tumor, bacterial, parasitic, viral, or auto antigens. Thus, the skilled artisan would understand how to modify the epitopes as claimed.

Claims 1, 3, 4 and 5 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action

states that the specification has not disclosed the structure of product reasonably enough which would convey they were in possession of what they consider to be their claimed invention. Applicants traverse.

Applicants submit that it would be clear to one skilled in the art, based on what is disclosed in the specification and what is known in the art, that the structure of the product is an HPV-L1 protein, modified as directed in the instant application to contain no T-cell directing epitopes and linked to a protein epitope which induces an antibody response. To this end, Applicants submit herein a reference (Nieland, J.D. *et al.*, 1999) which illustrates the capability of one skilled in the art at the time of the invention to perform the required procedures without undue experimentation.

According to Nieland *et al.*, it had been demonstrated in several animal models that HPV VLPs can induce type-specific high titered neutralizing antibodies against conformationally dependent L1-epitopes and confer antibody-dependent protection against experimental infection with wild-type virus. It was known that these VLPs could also efficiently induce a cytotoxic T-lymphocyte response. Nieland *et al.* thus concluded that the neutralizing antibodies are only effective for one specific virus type owing to the presence of a strongly immunodominant type-specific epitope (ITSE). Nieland *et al.* aimed to use ITSE-depleted VLPs and accomplished the removal of the neutralizing epitope by site-directed mutagenesis using basic techniques in molecular biology. Thus those skilled in the art would know both the epitopes to be removed and the method by which to remove them.

Thus, Applicants request that the rejections under 35 U.S.C. § 112 be withdrawn.

Claim Rejections under 35 U.S.C. § 102

Claims 1, 3, 4, 5 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Bloch *et al.* (WO 97/46693). Bloch *et al.* purportedly disclose a non-infectious virus-like particle (VLP) wherein the a region of the L1 is substituted for a second protein.

To prove anticipation under 35 U.S.C. §102, "...requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985).

Applicants respectfully assert that Bloch *et al.* is not directed towards a carrier capsid protein which has had an epitope removed by site-directed mutagenesis, but is in fact directed to a complete capsid comprising the HPV-L1 protein, wherein said protein has been altered by fusion with a number of other HPV capsid proteins. Additionally, the Bloch *et al.* specifically discloses capsids which, as specified in all claims of the invention, always contain a nucleic acid segment.

In contrast, the presently claimed invention is directed to the use of a single carrier protein, not a capsid comprising the protein, and is further directed to a fusion of this protein to another protein containing one or more T-cell epitopes. In this regard, Bloch *et al.* disclose only the possibility of partially deleted use of the L1 protein, and not with the

replacement of epitopes through site directed mutagenesis. Thus Bloch *et al.* do not recite the elements of the current claims.

Claims 1, 3, 4, 5 stand rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Gissmann *et al.* (WO 96/11272). Gissmann *et al.* purportedly disclose a structural protein of L1 wherein several sections have been deleted and still form virus like particles (VLPs) and which further were fused to a second peptide such as L2.

Applicants note that claim 1 of the present invention is directed to proteins wherein the conformational neutralizing epitopes which induce immunological reactions have been replaced through site-directed mutagenesis. In contrast, Gissmann *et al.* merely disclose proteins in which linear peptide sequences have been deleted, or which are used in part. The proteins of the present invention, which have been altered to remove conformational epitopes, are not disclosed by Gissmann *et al.* Thus Gissmann *et al.* do not anticipate the claims.

Claims 1, 3, 4, 5 stand rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Burger *et al.* (WO 99/48518). Burger *et al.* purportedly disclose a composition comprising a fusion protein that does not contain any papillomavirus non-specific epitopes and auxiliary agents and at least fusion protein is L1 and E protein of papillomavirus.

Applicants assert that Burger *et al.* disclose a fusion protein comprised of at least one L1 protein of one or more papillomaviruses and is also comprised of at least one E-

protein of one or more papilloma viruses, whereby the fusion protein does not contain any papilloma virus non-specific epitopes. Thus, the fusion protein of the cited reference contains only papillomavirus specific epitopes. In contrast, the exclusion of papillomavirus specific epitopes is essential to the presently claimed invention. Claim 1 of the present invention is concerned with removal of any T-cell epitopes specific to papillomaviruses from the HPV-L1 protein. Thus, this reference fails to recite the elements of the claimed invention.

Claim 1 stands rejected under 35 U.S.C. §102(a) as purportedly anticipated by Gissmann *et al.* (U.S. Patent No. 6,066,324). The claimed invention is purportedly anticipated by the product disclosed in any one of claims 1-8 of Gissmann *et al.*

Claim 1 of the present application is directed to HPV-L1 capsids which the HPV-L1 protein has been intentionally modified to remove major type-specific epitopes causing production of neutralizing antibodies. Modifications are achieved by amino acid substitutions. Such modified HPV-L1 protein may be in fusion with a peptide (of up to 60 amino acids in length) comprising one or more T-cell epitopes (*see* present claims 3-5).

In contrast, Gissmann *et al.* is specifically directed to amino acid deletions, not substitutions, as discussed above concerning the PCT application from which this patent is derived. Thus, Applicants submit that this reference does not recite the elements of the claimed invention.

Claims 1, 3, 4, and 5 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Bloch *et al.* (U.S. Patent No. 6,420,160). Bloch *et al.* purportedly disclose a non-infectious virus-like particle (VLP) wherein the region of the L1 is substituted for a second protein. The non-infectious L1 purportedly meets the "modified" limitation and the chimeric of L1 to E7 of claim 2 of Bloch *et al.* meets the "second peptide" limitations as well as the antigen comprising tumor and/or T cell epitope. As discussed above with regard to the rejection of claims over the PCT application from which this cited reference is derived, Bloch *et al.* are concerned only with an HPV-L1 capsid containing a nucleic acid molecule, not a protein lacking neutralizing epitopes linked to a peptide containing T-cell directing epitopes, as presently claimed. Thus, Bloch *et al.* fail to recite the elements of the claimed invention.

Claim 1 stands rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Gissmann *et al.* (U.S. Patent No. 6,361,778). Gissmann *et al.* purportedly disclose a modified L1 protein. Applicants submit that Gissmann *et al.* is solely directed towards those proteins which have been modified by deletion of peptide sequences, not by the replacement of sequences to remove conformational epitopes as currently claimed.

Claim 1 stands rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Gissmann *et al.* (U.S. Patent No. 6,066,324). Gissmann *et al.* purportedly disclose a modified L1 protein. As discussed above, this reference fails to recite all the elements of

the claimed invention because it does not disclose peptides whose epitopes have been replaced, but rather discusses peptides which have been used in part or altered by deletion of peptides or peptide sequences.

Finally, Applicants note that according to M.P.E.P. §706.02, when the when rejecting claims under 35 U.S.C. §102, the Examiner is instructed to choose either section (a), (b), or (e) under which to site a given reference. However, in the interest of expediting prosecution, Applicants have addressed all of the rejections cited in the outstanding Office Action.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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